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Corticospinal excitability is enhanced after visuomotor adaptation and depends on learning rather than performance or error

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Bagce HF, Saleh S, Adamovich SV, Krakauer JW, Tunik E. Corticospinal excitability is enhanced after visuomotor adaptation and depends on learning rather than performance or error. *J Neurophysiol* 109: 1097–1106, 2013. First published November 28, 2012; doi:10.1152/jn.00304.2012.—We used adaptation to high and low gains in a virtual reality setup of the hand to test competing hypotheses about the excitability changes that accompany motor learning. Excitability was assayed through changes in amplitude of motor evoked potentials (MEPs) in relevant hand muscles elicited with single-pulse transcranial magnetic stimulation (TMS). One hypothesis is that MEPs will either increase or decrease, directly reflecting the effect of low or high gain on motor output. The alternative hypothesis is that MEP changes are not sign dependent but rather serve as a marker of visuomotor learning, independent of performance or visual-to-motor mismatch (i.e., error). Subjects were required to make flexion movements of a virtual forefinger to visual targets. A gain of 1 meant that the excursions of their real finger and virtual finger matched. A gain of 0.25 (“low gain”) indicated a 75% reduction in visual versus real finger displacement, a gain of 1.75 (“high gain”) the opposite. MEP increases (>40%) were noted in the tonically activated task-relevant agonist muscle for both high- and low-gain perturbations after adaptation reached asymptote with kinematics matched to veridical levels. Conversely, only small changes in excitability occurred in a control task of pseudorandom gains that required adjustments to large errors but in which learning could not accumulate. We conclude that changes in corticospinal excitability are related to learning rather than performance or error.

sensorimotor cortex; primary motor cortex; transcranial magnetic stimulation; motor evoked potential; virtual reality

THE PERFORMANCE VERSUS LEARNING distinction is a particularly vexing issue when studying changes in the brain after training in healthy subjects or in patients (Krakauer 2007). One approach to assessing the state of the motor system is to measure corticospinal excitability with transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEPs) (Pascual-Leone et al. 1994, 1995; Muellbacher et al. 2001). MEPs serve both as an assay for internal changes in inhibitory/excitatory balance that cannot be accessed directly and as a measure of the integrity of a motor output pathway. For example, a lower conduction time (Vang et al. 1999), a higher baseline MEP amplitude (Rapisarda et al. 1996), and a greater change in MEP

amplitude (Koski et al. 2004; Swayne et al. 2008) after stroke are thought to be beneficial to voluntary action, i.e., performance. Alternatively, increases in MEP have been associated with motor learning (Cirillo et al. 2011; Gallasch et al. 2009; Jensen et al. 2005; Koeneke et al. 2006) rather than changes in motor output, although in these studies the learning-related changes in performance were not controlled for. One study, however, demonstrated that as subjects learned to increase peak pinch force to maintain a target electromyographic (EMG) profile, motor cortex excitability scaled up in a linear fashion (Muellbacher et al. 2001). On follow-up measurements, MEP amplitude returned to baseline levels but subjects retained the learned peak force profile, which suggested that the increased MEP was not necessary to maintain performance but instead was associated with learning. Alternative explanations for the excitability changes in this study are possible, however. One is that the transient increase in MEP amplitude was a result of the ramping up of force (i.e., motor output) from low to high (versus high to low) during adaptation, rather than learning per se. Another potential explanation is that the increased excitability was the result of error: once the mismatch between produced and optimal force was zero, excitability normalized. Thus whether excitability changes are truly learning related rather than related either to the direction of the change in the magnitude of motor output or to errors remains unresolved.

Here we sought to test directly whether learning affects corticospinal excitability, independent of performance or error, by studying gain adaptation of finger movements in a novel virtual reality (VR) environment. Gain adaptation is ideally suited to testing the competing hypotheses that changes in M1 excitability relate to changes in performance or error versus that they relate to learning. In the low-gain condition (gain = 0.25) a 75% reduction in visual versus real finger displacement occurs, requiring an increase in finger excursion, whereas the high-gain condition (gain = 1.75) results in the opposite. It has been shown that some motor cortical cells linearly scale firing rate with speed and distance (Paninski et al. 2004). As a gain change requires either a higher or a lower peak velocity and displacement for a given visual excursion compared with baseline, M1 excitability changes might reflect changes in firing rate. That there is a relationship between excitability and firing rate has been known from classic animal studies investigating the effect of anodal DC current on motor cortex

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(Bindman et al. 1964; Creutzfeldt et al. 1962; Purpura and McMurtry 1965).

In this study, we measured MEPs with the assumption that any modulation of corticospinal excitability following adaptation represents an excitability change at the level of primary motor cortex, as recent animal studies suggest that the locus of learning-related synaptogenesis and reorganization is in M1 and not at spinal-level synapses (Adkins et al. 2006; Kleim et al. 2002; Remple et al. 2001). If excitability changes parallel the performance change required by the visuomotor gain relationship, then excitability should increase for the low-gain condition and decrease for the high-gain condition. If, however, excitability is a marker for motor learning, then excitability increases should be seen for both gain conditions.

MATERIALS AND METHODS

Subjects

Nine subjects participated in *experiment 1* (5 men, 4 women; mean \pm SD age 25.9 ± 4.6 yr), 9 in *experiment 2* (5 men, 4 women; 29.2 ± 7.0 yr), 6 in *experiment 3* (4 men, 2 women; 32.0 ± 6.9 yr), and 14 in *experiment 4* (9 men, 5 women; 26.8 ± 6.2 yr). All subjects were right-handed (Oldfield 1971) and free of neurological or orthopedic conditions that could interfere with the experiment, were safe to receive TMS (Keel et al. 2000), and provided written and verbal institutionally informed consent. All protocols were approved by the Institutional Review Board of the University of Medicine and Dentistry of New Jersey.

Setup

Subjects were seated with forearms (semipronated) and hands hidden from direct line of sight under a widescreen monitor oriented horizontally (Fig. 1B). Real-time visual feedback of hand motion was conveyed on the monitor as motion of VR-rendered hand models (Virtools software; Dassault Systems) actuated by kinematic data streaming from data gloves (5DT-16MRI) worn by subjects. The display was angled and magnified such that VR hand size, position, and orientation matched a first-person perspective vantage.

Task

Upon a visual cue, subjects flexed the right index finger metacarpophalangeal (MCP) joint to a virtual target represented on the screen as an arrow (i.e., subjects were asked to completely cover the virtual arrow with the virtual finger) and then returned to a fully extended position. Subjects were asked to complete the task as fast as possible, but without sacrificing accuracy or precision. Each trial lasted 3.5 s (intertrial rest interval: 2.5 s). Depending on the experiment (see below), the motion of the VR hand was scaled in real time relative to the kinematic data streaming from the glove. One of three scaling factors was applied to the VR hand motion: 1.00 (G1.00, veridical), in which virtual hand motion corresponded to actual motion, 0.25 (G0.25), in which virtual hand motion was 25% of actual motion, and 1.75 (G1.75), in which virtual hand motion was 175% of actual motion (Fig. 1A). Thus a 45° actual movement would produce a virtual movement of 11.25° (G0.25), 45° (G1.00), or 78.75° (G1.75).

Experiment 1. This experiment tested for changes in corticospinal excitability following a block of adaptation to low-gain visual feedback. Subjects performed the task in three blocks. Feedback was G1.00 in *block 1* and *block 3* and G0.25 in *block 2* (Fig. 1C, top). Each block consisted of 42 movements performed toward three physical angles (45°/65°/85°, 14 trials per angle). Three targets were used to keep subjects engaged in the task. To ensure that any change in excitability could be attributed to a learned remapping and not just

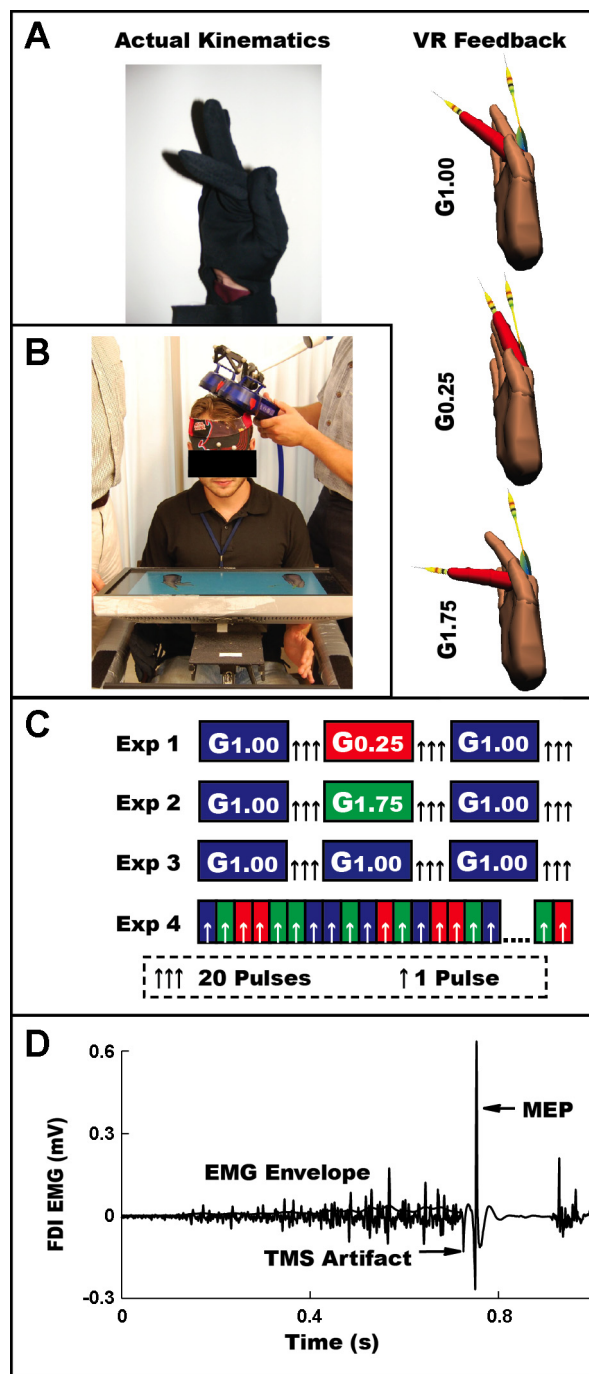


Fig. 1. A: actual finger position (left) and virtual finger position (right) for a single 45° physical angle. Physical angle (performance) was identical and virtual angle (feedback) was augmented (in real time) for each condition within each experiment. Virtual target arrows (for *experiments 1, 2, and 3*) and virtual finger color change (*experiment 4*) are shown. VR, virtual reality. B: virtual reality setup. C: condition and trial structure for each experiment. Motor evoked potential (MEP) acquisition is indicated by arrows either after a block of movements (*experiments 1, 2, 3*) or during a given trial (*experiment 4*). D: raw and filtered/rectified (thin line) EMG signal acquired from a typical subject in *experiment 4*. FDI, first dorsal interosseus; TMS, transcranial magnetic stimulation.

changes in movement amplitude, movements were kinematically clamped, which is to say that subjects' physical target angles were 45°, 65°, and 85° at the end of adaptation. This was achieved through systematic manipulation of the perceived angular position of the target

in virtual space: it was either kept the same (G1.00 blocks: 45°/65°/85°) or adjusted to be of smaller visual excursion (G0.25 block: 11.25°/16.25°/21.25°). As detailed below, MEPs were measured after each movement block.

Experiment 2. This experiment tested for changes in corticospinal excitability following a block of adaptation to high-gain visual feedback. The protocol was similar to *experiment 1*, except here movement amplitude in all three blocks was clamped at 20°/30°/40°, with visual excursion reaching 20°/30°/40° in G1.00 and 35°/52.5°/70° in G1.75. The nature of the high-gain visual feedback was the reason why different movement amplitudes were used in *experiment 2*. For example, implementing an 85° movement amplitude in *experiment 2* would have required an unnatural 148.75° virtual joint angle.

Experiment 3. This was a control experiment to address the potential confound that changes in MEPs might relate to progressive increases in peak velocity (i.e., motor output) associated with gain adaptation rather than learning per se. Subjects performed movements with veridical feedback in three separate blocks. During *blocks 1* and *3* (B1G1.00, B3G1.00), subjects made 42 movements to one of three pseudorandomly presented target angles (35°/45°/55°). During *block 2* (B2G1.00), on the other hand, the target angle was increased from 10° to 55°, simulating a “ramping up” of motor output throughout the block. To prevent subjects from anticipating subsequent targets during *block 2*, angles of 5° increments were pseudorandomly presented in a progressively increasing fashion throughout *block 2* (i.e., 10° . . . 20° . . . 15° . . . 30° . . .). The last 10 trials during *block 2* were identical to *blocks 1* and *3*, ensuring that subjects reached similar asymptotic levels of motor output.

Experiment 4. The block experiments described above were designed to test the hypothesis that corticospinal excitability changes are the result of accumulated learning rather than motor output. A counterhypothesis would be that these changes arise because of perceived errors and their associated corrections. This control experiment tested excitability during trial-by-trial error correction in the absence of a constant systematic perturbation that would allow accumulation of learning. Subjects flexed the MCP joint over a single block (66 total trials). In pseudorandomly interleaved trials, feedback was G1.00, G0.25, or G1.75 (22 trials/condition). In this experiment, an explicit visual target was not presented to the subjects at the beginning of each trial, as was the case in *experiments 1, 2, and 3*. Rather, subjects were instructed to produce movements to a kinesthetically defined 45° target angle. To aid subjects in identifying the end of movement, the virtual finger turned red when subjects achieved the 45° angle. Preplanned movements to a proprioceptive 45° target angle minimized between-condition differences in kinematic traces during the early phase of the trial, while still allowing subjects enough time to fully perceive the altered visuomotor feedback. As the subjects initiated movement, however, they were expected to adjust kinematics online in response to the altered visuomotor feedback. Compare *experiment 4* to *experiments 1–3*, in which explicit visual feedback of the target was provided at the very beginning of the trial, allowing subjects in *experiments 1–3* to preplan movements to various visual target angles.

Neuronavigated Transcranial Magnetic Stimulation

Single-pulse TMS (Magstim Rapid2, 70-mm double AFC coil) was applied at 110% resting motor threshold [minimum intensity required to elicit MEPs > 50 μ V in the right first dorsal interosseous (FDI) muscle on 5/10 consecutive trials]. Each subject's high-resolution anatomical MRI scan (3T Siemens Allegra) was used to render a three-dimensional cortical surface. Fiducial locations on the MRI were coregistered with the subject's head to allow frameless neuro-navigation (Visor; Advanced Neuro Technology). The stimulated “hotspot” of motor cortex was marked on the MRI scan. The coil was held tangentially with the handle facing posteriorly 45° off the sagittal plane and was tracked online to be over the hotspot.

Experiments 1, 2, and 3. Twenty MEPs were recorded immediately after each block over a period of 2 min. To maintain consistent EMG activity across trials and conditions, subjects were asked to lightly squeeze a force transducer (FlexiForce; Tekscan). Force feedback was displayed on the monitor as a rectangular horizontal bar. TMS was triggered by a TTL signal when a target force of 2.5 ± 0.25 N was maintained over a period of 100 ms. This particular target force was used because the EMG activity required to attain this force level matched the EMG activity produced in *experiment 4*, allowing us to draw direct comparisons between the results of these experiments and *experiment 4*.

Experiment 4. MEPs were recorded during each movement. TMS was triggered by a TTL when the MCP angle reached 40° (i.e., immediately prior to reaching the 45° target angle). Keeping joint angle constant at the time of MEP measurement ensured that between-condition MEP differences would not be confounded by discrepancies in muscle length-dependent stretch reflexes (Raptis et al. 2010).

Analysis

Kinematics. The MCP joint angle data were filtered (2nd-order Butterworth: 10-Hz low pass) and analyzed off-line with custom-written MATLAB software (The MathWorks). For each trial, movement onset and offset were defined as the time at which the angular velocity exceeded and fell below 5% of peak angular velocity for >60 ms. In *experiments 1, 2, and 3*, peak angular velocity served as a marker of performance because it reliably represented subjects' adaptation to the visuomotor discordance. In *experiment 4*, instantaneous angular velocity (at the time of TMS stimulation) and the peak initial angular acceleration within 100 ms of movement onset were analyzed as performance parameters. Angular acceleration was analyzed on trials following each condition (“ $n + 1$ ” trials) to determine whether online adaptation had affected forward planning on subsequent trials.

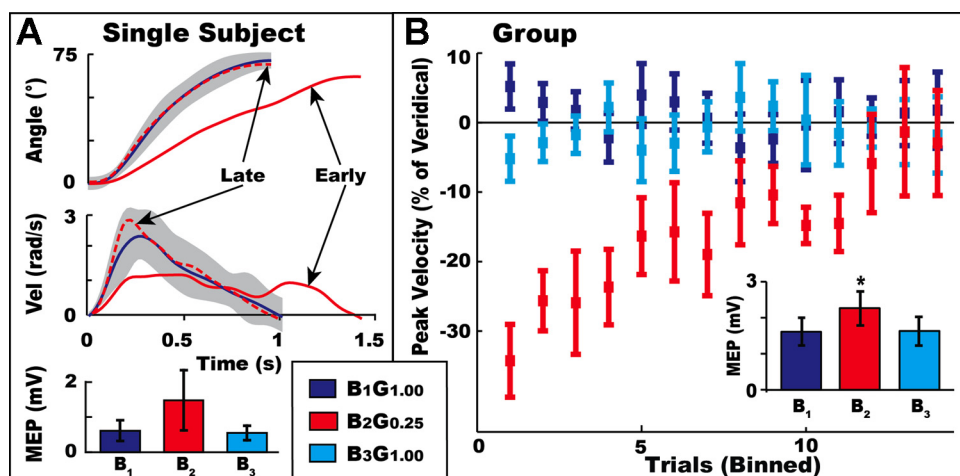
Electrophysiology. EMG activity of the FDI and abductor digiti minimi (ADM) muscles was acquired with a 4-Channel Bagnoli EMG System (Delsys). Raw analog EMG signal was amplified ($\times 10$), streamed to a data acquisition card (NI USB-6221, National Instruments, 2-kHz sampling frequency), and analyzed off-line with custom-written MATLAB software. We computed 1) MEP, the peak-to-peak amplitude of the EMG signal 20–50 ms after the TMS pulse (Fig. 1D), and 2) background EMG, calculated after filtering (2nd-order Butterworth: 5- to 250-Hz band pass, 55- to 65-Hz notch), full-wave rectifying, and enveloping (20-Hz low pass) the EMG signal. From this, the average EMG signal 50 ms preceding TMS stimulation was extracted for analysis. Because empirical data suggest that background EMG covaries with MEP amplitude for dynamic, low-force contractions (Aranyi et al. 1998; Kasai and Yahagi 1999; Ni et al. 2006) such as those used in our protocol, we compared background EMG levels across conditions (Datta et al. 1989; Flament et al. 1993) to ensure that between-condition differences in MEP amplitude were due to learning and not confounded by motor output.

Coil position. To ensure that coil position did not differ among conditions, a three-dimensional coil position error was calculated as the distance between TMS coil position at the time of stimulation and the hotspot.

Statistics

Electrophysiological variables (MEP, EMG) were averaged across trials for each condition and subject. Means were submitted to a repeated-measures analysis of variance (rmANOVA). For kinematic analysis of *experiments 1* and *2* a three-way rmANOVA with factors [levels]: time [early, late], target [angle1, angle2, angle3], and condition [B1Veridical, B2Gain, B3Veridical] was calculated. The first and last trials for each angle of each condition were used for the “early” and “late” data, respectively. For kinematic analysis of *experiment 3*,

Fig. 2. Kinematic and electrophysiological data in *experiment 1*. *A* (subject): blue line and shaded region represent the mean (\pm SD) metacarpophalangeal (MCP) flexion angle (*top*) and peak angular velocity (*middle*) for a typical subject, averaged across B1G1.00 and B3G1.00. Mean traces of the first 3 (early, solid red) and last 3 (late, dashed red) trials of B2G0.25 are superimposed. Mean (\pm SD) MEP bar plot (*bottom*) for this subject demonstrates increased M1 facilitation immediately after B2G0.25 relative to B1G1.00 and B3G1.00. *B* (group): group mean (\pm SE) peak velocity as % change relative to the average veridical trials for each angle for each block. Trials for all 3 target angles are binned together; thus the 42 total trials are represented by 14 bins on the *x*-axis. Subjects adapted to B2G0.25 by normalizing movement velocity to the level observed in the veridical blocks. Also shown (*inset*) is group mean (\pm SE) MEP.



a one-way rmANOVA with levels [B1Veridical, B2Veridical, B3Veridical] was calculated for both early- and late-stage adaptation, in which the average of the first and last three trials was used for the early and late data, respectively. Finally, a mixed linear regression model was also performed for *experiment 4* to characterize the degree to which each variable contributed to the MEP effect. For this, MEP was defined as the dependent variable and coil displacement error, background EMG, angular velocity, and gain feedback (G0.25, G1.75) as independent variables. Data were analyzed with PASW Statistics 18 (SPSS). rmANOVA was used to test for main effects and interactions. Statistically significant interaction effects were tested post hoc by Tukey's honestly significant difference (HSD) test. Significance threshold was set at $P < 0.05$.

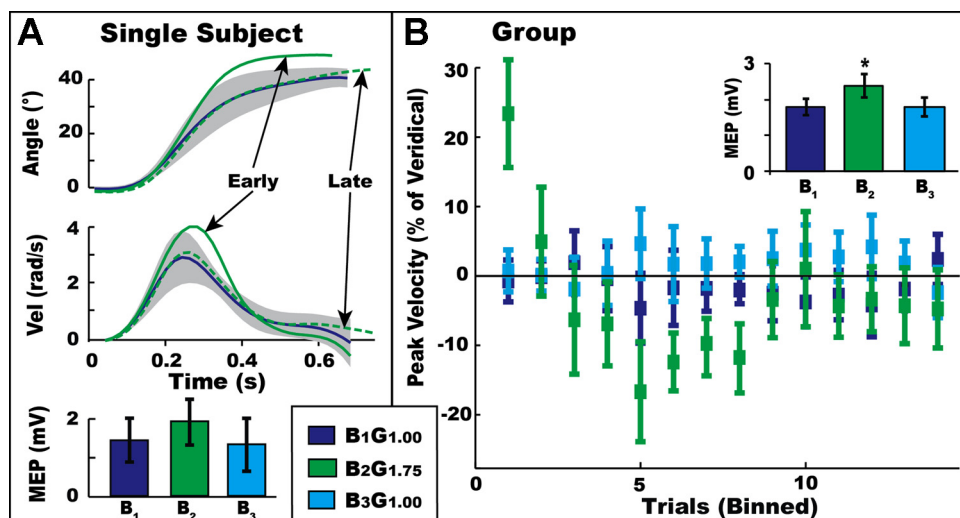
RESULTS

Excitability Increased After Gain Adaptation

Subjects showed complete adaptation to visuomotor gain when visual motion of the VR finger was scaled to either 25% (*experiment 1*, G0.25 condition) or 175% (*experiment 2*, G1.75 condition) of actual finger motion. Figure 2*A* (*experiment 1*) and Figure 3*A* (*experiment 2*) show a representative subject's mean joint angle (*top*) and angular velocity (*middle*) traces for early and late adaptation stages. While early adaptation was characterized by initial hypometria (*experiment 1*) or hyper-

metria (*experiment 2*) with subsequent online adjustments, finger position traces during late adaptation were comparable to those in the veridical block. For kinematic analysis of *experiments 1* and *2* a three-way rmANOVA with factors [levels]: time [early, late], target [angle1, angle2, angle3], and condition [B1Veridical, B2Gain, B3Veridical] was calculated. The first and last trials for each angle of each condition were used for the early and late data, respectively. For kinematic analysis of *experiment 3*, a one-way rmANOVA with levels [B1Veridical, B2Veridical, B3Veridical] was calculated for both early- and late-stage adaptation, in which the average of the first and last three trials was used for the early and late data, respectively. It should be noted that in *experiment 2* there was a significant drop in peak velocity below baseline at around *trial 8* (see 3rd time bin in Fig. 3*B*), likely due to subjects' tendency in early trials to overshoot the visual target but in later trials to adjust online kinematics by moving at a slower speed. We quantified the degree of adaptation by calculating the peak velocity in each trial. Figure 2*B* and Figure 3*B* show similar behavior at the group level, in which subjects progressively adapted their peak velocity to match that of the veridical blocks. As expected, rmANOVA revealed a significant main effect of target angle on peak velocity for both the low- and high-gain learning paradigms (*experiment 1*: $F_{2,16} = 122.41$,

Fig. 3. Subject (*A*) and group (*B*) kinematic and electrophysiological data in *experiment 2*. Labels are as in Fig. 2.



$P < 0.001$; *experiment 2*: $F_{2,16} = 40.73$, $P < 0.001$). Notably, a significant main effect of visual feedback condition on peak velocity was observed for both the low- and high-gain learning paradigms (*experiment 1*: $F_{2,16} = 11.94$, $P = 0.002$; *experiment 2*: $F_{2,16} = 4.36$, $P = 0.038$), and, as displayed in Figs. 2B and 3B, the time \times condition interaction effect was also significant (*experiment 1*: $F_{2,16} = 5.552$, $P = 0.016$; *experiment 2*: $F_{2,16} = 5.29$, $P = 0.023$). To confirm that the observed effects were a result of learning, we averaged raw velocities across all three angles and performed two separate one-way rmANOVAs for both the early and late interactions. Subanalysis revealed a significant main effect of visual feedback condition on peak velocity during the early stage of adaptation (*experiment 1*: $F_{2,16} = 20.208$, $P < 0.001$; *experiment 2*: $F_{2,16} = 6.438$, $P = 0.011$); however, similar effects were not seen during the latter phase of each block (*experiment 1*: $F_{2,16} = 1.073$, $P = 0.363$; *experiment 2*: $F_{2,16} = 1.171$, $P = 0.334$), suggesting that subjects fully adapted to the visuomotor gain. Post hoc pairwise comparison confirmed that velocity effects were driven by significant differences between the early gain block and first veridical block (Tukey's corrected; *experiment 1*: $t_8 = -4.038$, $P = 0.001$; *experiment 2*: $t_8 = 3.4685$, $P = 0.004$) but not between the two veridical blocks (Tukey's corrected; *experiment 1*: $t_8 = -2.277$, $P = 0.10$; *experiment 2*: $t_8 = -0.294$, $P = 0.221$). Overall, these findings demonstrate that kinematic performance in finger space after adaptation was similar to that seen before adaptation.

MEPs were measured in the FDI muscle for a period of 2 min following each training block. Representative subject (Figs. 2A and 3A) and group data (Figs. 2B and 3B) demonstrate that corticospinal excitability was increased for a period of 2 min after adaptation to both low- and high-gain feedback (mean percent change \pm SE: *experiment 1*: $53.3 \pm 16.2\%$; *experiment 2*: $40.9 \pm 17.1\%$) relative to the veridical. rmANOVA confirmed a significant MEP effect for both experiments (*experiment 1*: $F_{2,16} = 4.618$, $P = 0.026$; *experiment 2*: $F_{2,16} = 4.901$, $P = 0.042$). Post hoc pairwise comparisons revealed that the effects were driven by significant differences between MEPs following the adaptation block and MEPs following the first veridical block (Tukey's corrected; *experiment 1*: $t_8 = 2.694$, $P = 0.044$; *experiment 2*: $t_8 = 2.511$, $P = 0.038$) but not when comparing MEPs following the first and second veridical blocks (Tukey's corrected; *experiment 1*: $t_8 = -0.035$, $P = 0.999$; *experiment 2*: $t_8 = -0.021$, $P = 1.000$). No significant between-condition differences were noted in background EMG activity (*experiment 1*: $F_{2,16} = 2.321$, $P = 0.147$; *experiment 2*: $F_{2,16} = 0.647$, $P = 0.519$), suggesting that any difference in motor output could not account for the MEP effects.

We performed a post hoc subanalysis of MEPs collected after the low-gain (*experiment 1*) and high-gain (*experiment 2*) blocks to discern whether postadaptation increases in excitability were relatively stable over the entire 2 min of MEP data collection. Pairwise t -tests revealed nonsignificant differences between the first and last 10 MEPs following both the low-gain block (MEP \pm SE: early: 2.27 ± 0.48 mV; late: 2.26 ± 0.47 mV, $t_8 = 0.070$, $P = 0.946$) and the high-gain block (MEP \pm SE: early: 2.63 ± 0.44 mV; late: 2.30 ± 0.37 mV, $t_8 = 1.286$, $P = 0.234$), suggesting that only a slight drop in excitability occurred during the second half of MEP data collection.

We performed a second post hoc analysis on MEP and EMG variance to ensure that the above effects were not driven by outlier trials. For this, the variance of these two outcome measures (MEP and EMG) was calculated for each experiment (*experiment 1* and *experiment 2*) for each subject (*S1* through *S9*) for each condition (veridical-gain-veridical). Variances were submitted to a rmANOVA, which confirmed no significant main effect of condition on MEP variance (*experiment 1*: $F_{2,16} = 0.16$, $P = 0.850$; *experiment 2*: $F_{2,16} = 1.50$, $P = 0.253$) or EMG variance (*experiment 1*: $F_{2,16} = 1.49$, $P = 0.255$; *experiment 2*: $F_{2,16} = 0.88$, $P = 0.432$).

Finally, to ensure an appropriate sampling size for the remaining experiments (*experiments 3* and *4*), we performed a sample-size calculation for the two primary outcome variables (MEPs and angular velocity) of *experiments 1* and *2*, using an ANOVA with a significance threshold set to 0.05 and a power of 0.8. To be more conservative, we used data from the high-gain adaptation experiment (*experiment 2*), which had the smaller effects in both variables. For an effect size of 2.61 [MEPs: $(2.38 - 1.78)/0.23$] and 4.15 [velocity: $(2.32 - 1.78)/0.13$], the sample-size calculation indicated a minimum of 5 and 3 subjects, respectively, to yield significant effects.

Control Experiment: "Ramping Up" Motor Output Did Not Augment Excitability

We performed a control experiment (*experiment 3*) to rule out the possibility that the postadaptation M1 excitability increases observed in *experiments 1* and *2*, which were in the same direction (increases), were the result of the similar "ramping up" of peak velocity (i.e., motor output) to the final asymptotic level. Figure 4 shows that peak velocity in B2G1.00 pseudorandomly increased to the asymptotic level of B1G1.00 and B3G1.00 (velocity early: $F_{2,10} = 30.632$, $P < 0.001$; velocity late: $F_{2,10} = 1.300$, $P = 0.309$). Figure 4, *inset*, shows that when M1 excitability was probed at the end of each block we observed no between-block MEP effects ($F_{2,10} = 0.605$, $P = 0.565$), suggesting that increases in M1 excitability

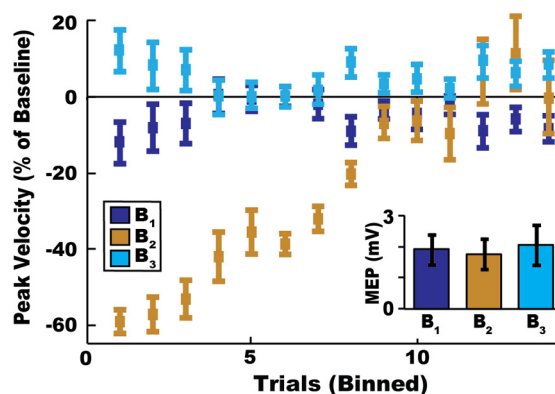


Fig. 4. Kinematic and electrophysiological data in control *experiment 3* (see MATERIALS AND METHODS). Labels are as in Fig. 2B. Gold color shows the incrementally increasing angular velocity over the course of the block, without any requirement for visuomotor adaptation (as was necessary in *experiments 1* and *2*). Note the absence of any modulation of M1 excitability at the group level (*inset*).

Table 1. Summary of group mean kinematic and electrophysiological data for experiment 1 (low-gain adaptation)

	B ₁ G _{1.00}	B ₂ G _{0.25}	B ₃ G _{1.00}
MEP, mV	1.615 ± 0.382	2.262 ± 0.473	1.625 ± 0.394
EMG, mV	0.031 ± 0.005	0.037 ± 0.007	0.030 ± 0.004
Vel, rad/s			
Early	2.189 ± 0.134	1.614 ± 0.106	2.464 ± 0.096
Late	2.692 ± 0.220	2.418 ± 0.222	2.719 ± 0.268

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential after the motor task; EMG, background electromyographic activity immediately before the MEP; Vel, peak angular velocity. Peak velocity is averaged across all 3 target angles.

observed in experiments 1 and 2 were a result of visuomotor learning rather than associated changes in motor performance (see Tables 1–4).

Control Experiment: Observed Errors and Their Associated Corrections Did Not Augment Excitability

We observed increases in corticospinal excitability after the low- and high-gain conditions independent of performance. The possibility remains that these changes in excitability resulted from a period of observing and correcting errors in extent rather than learning the gains themselves. Experiment 4 was designed to address this possibility. Subjects were exposed to a block of trials in which they had to make finger flexion movements to a 45° physical angle. Three different visual gains were pseudorandomly interleaved across trials: veridical (G1.00), low gain (G0.25) or high gain (G1.75). Figure 5A shows a typical subject's mean joint angle (*top*) and angular velocity (*middle*) trace for each condition. Instantaneous angular velocity immediately prior to the TMS pulse (i.e., at 40° flexion) was calculated to confirm that subjects showed kinematic evidence of a differential response to the gain changes. At the group level (see Fig. 5B, *left*), angular velocity significantly differed between conditions ($F_{2,26} = 18.843$, $P < 0.001$), with post hoc pairwise comparisons revealing that subjects significantly sped up in the G0.25 condition (group mean = 1.996 rad/s, $t_{13} = 3.187$, $P = 0.007$) and slowed down in the G1.75 condition (1.531 rad/s, $t_{13} = 4.270$, $P = 0.001$), relative to the veridical condition (G1.00: 1.822 rad/s). Thus subjects were seeing large errors in every trial and attempted to correct them. We confirmed this further by analyzing peak angular acceleration in the first 100 ms of the subsequent ($n + 1$) trial (i.e., before visual feedback contaminated the feedforward plan developed in the n trial). Significant differences were noted for the $n + 1$ trials (mean ± SE for G1.00, G0.25,

Table 2. Summary of group mean kinematic and electrophysiological data for experiment 2 (high-gain adaptation)

	B ₁ G _{1.00}	B ₂ G _{1.75}	B ₃ G _{1.00}
MEP, mV	1.778 ± 0.229	2.380 ± 0.327	1.781 ± 0.261
EMG, mV	0.054 ± 0.012	0.061 ± 0.013	0.051 ± 0.009
Vel, rad/s			
Early	1.780 ± 0.130	2.317 ± 0.148	1.825 ± 0.088
Late	1.971 ± 0.173	1.857 ± 0.192	2.031 ± 0.145

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential after the motor task; Vel, peak angular velocity. Peak velocity is averaged across all 3 target angles.

Table 3. Summary of group mean kinematic and electrophysiological data for experiment 3 (asymptote control)

	B ₁ G _{1.00}	B ₂ G _{1.00}	B ₃ G _{1.00}
MEP, mV	1.894 ± 0.484	1.746 ± 0.485	2.036 ± 0.640
Vel, rad/s			
Early	2.139 ± 0.222	1.002 ± 0.125	2.805 ± 0.338
Late	3.131 ± 0.434	3.362 ± 0.500	3.725 ± 0.479

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential after the motor task; Vel, peak angular velocity.

and G1.75: 12.6 ± 1.1 rad/s², 13.3 ± 1.1 rad/s², 11.5 ± 0.9 rad/s²; $F_{2,26} = 4.418$, $P = 0.023$), with post hoc comparisons demonstrating a slight, although nonsignificant, increase in acceleration for post-G0.25 trials ($t_{13} = 1.25$, $P = 0.232$) and a slight decrease for post-G1.75 trials ($t_{13} = 1.58$, $P = 0.139$), relative to post-G1.00 but a significant difference between post-G0.25 and post-G1.75 trials ($t_{13} = 3.14$, $P = 0.008$). This suggests that subjects partially preplanned movements based on the feedback they received in the previous trial. A control analysis of the same kinematic variable for trials preceding the G1.00, G0.25, and G1.75 ($n - 1$) trials, as expected, did not show this effect (12.0 ± 0.9 , 12.6 ± 1.1 , 12.8 ± 1.1 rad/s²; $F_{2,26} = 1.897$, $P = 0.174$). These kinematic analyses revealed that subjects were overtly responding online to the observed visual errors and partially adapting to each perturbation, evidenced by the $n + 1$ analysis, although they never reached full adaptation because of the pseudorandom ordering of the trials.

MEPs were evoked online as the subjects' actual MCP angle reached 40°. Figure 5A, *bottom* (typical subject), and Fig. 5B, *right* (group mean), show that MEP amplitude was affected by visual feedback (main effect: $F_{2,26} = 5.934$, $P = 0.008$). Post hoc pairwise comparisons confirmed that the 12.1% (±2.9) MEP increase was significant in the G0.25 over the G1.00 condition ($t_{13} = 2.965$, $P = 0.011$) but not between the G1.75 and G1.00 conditions ($P = 0.993$). Thus only small MEP effects were seen in the trial-by-trial experiment compared with the blocked paradigm despite larger perceived errors and continuous corrections in velocity. The effect seen in the low-gain condition is likely a small learning effect because we still found a small MEP effect after binning velocity across conditions. To do this, G0.25 trials with velocities exceeding 1 SD and G1.75 trials with velocities below 1 SD of each individual subject's global mean velocity were excluded from analysis (rmANOVA for angular velocity after trial exclusion: $F_{2,26} = 1.080$, $P = 0.348$). Despite equalized velocity across all three visual feedback

Table 4. Summary of group mean kinematic and electrophysiological data for experiment 4 (trial-by-trial control)

	G _{1.00}	G _{0.25}	G _{1.75}
MEP, mV	2.175 ± 0.538	2.392 ± 0.556	2.182 ± 0.534
EMG, mV	0.039 ± 0.005	0.042 ± 0.006	0.040 ± 0.006
Vel, rad/s	1.822 ± 0.165	1.996 ± 0.159	1.531 ± 0.181

Values are group mean (±SE) kinematic and electrophysiological data. MEP, motor evoked potential during the motor task; Vel, instantaneous angular velocity.

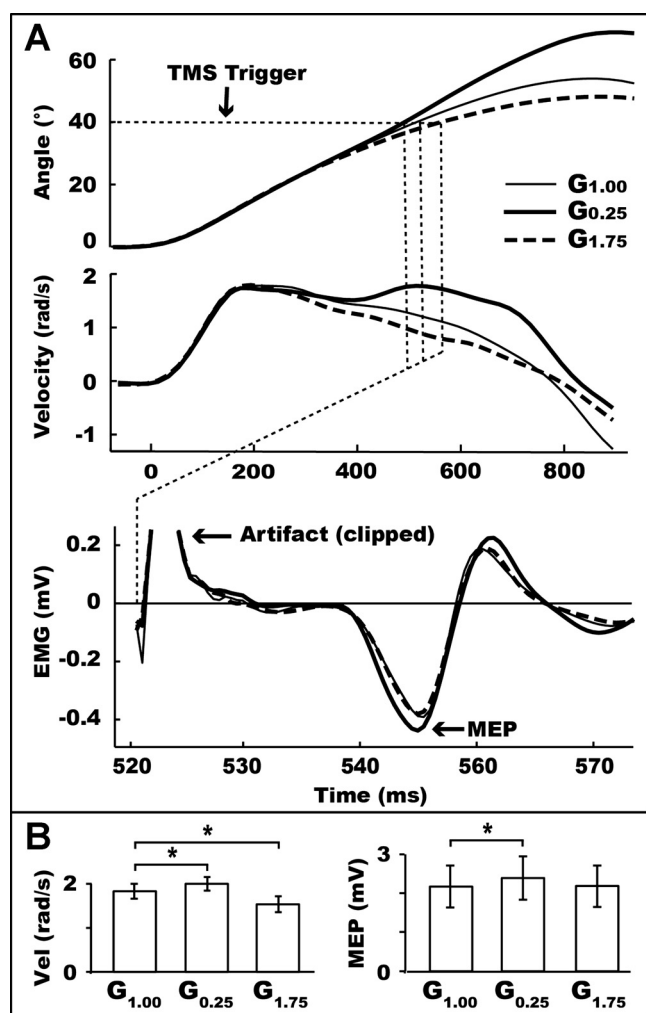


Fig. 5. Kinematic and electrophysiological data in *experiment 4*. *A* (subject): mean MCP flexion angle (*top*) and angular velocity (*middle*) for G1.00, G0.25, and G1.75 trials. *Bottom*: the same subject's mean MEP traces, which have been realigned in time according to when TMS was triggered. Dotted line marks the time at which the subject attained a 40° flexion angle, resulting in a trigger to signal the TMS pulse. *B* (group): mean (\pm SE) instantaneous angular velocity (*left*) and MEP (*right*). Asterisk denotes significant effects in a 1-sample paired *t*-test. To rule out velocity-based confounds on MEPs, data were reanalyzed by excluding G0.25 trials in which angular velocity exceeded 1 SD of the global mean velocity and, similarly, excluding G1.75 trials in which velocity was below 1 SD of the global mean. Blinded reanalysis of MEP data after velocity equalization revealed that MEPs were unaffected.

conditions, MEP amplitude remained 12.2% higher in the G0.25 condition (rmANOVA for MEP after trial exclusion: $F_{2,26} = 3.931$, $P = 0.038$).

To characterize the relative contribution of each independent variable to MEP amplitude, we performed a mixed linear regression analysis. MEPs were significantly correlated with expected variables such as coil displacement error ($\beta = -0.194$, $P < 0.001$), background EMG ($\beta = 0.212$, $P = 0.001$), and the G0.25 condition ($\beta = 0.120$, $P = 0.003$) but not with angular velocity ($\beta = 0.041$, $P = 0.262$) or the G1.75 condition ($\beta = -0.057$, $P = 0.171$). No significant between-condition differences were noted in background EMG activity ($P = 0.406$), suggesting that MEP effects were not confounded by differences in motor output.

Accuracy of TMS Stimulation

The three-dimensional error between the coil's position at the time of stimulation and the M1 hotspot was not significantly different between conditions (*experiment 1*: $P = 0.286$; *experiment 2*: $P = 0.155$), suggesting that MEP measurements were elicited from a consistent region of M1.

DISCUSSION

Here we tested whether changes in corticospinal excitability are related to learning, changes in performance (motor output), or motor error. We found increases in excitability for both low and high gains, rather than an increase and a decrease, respectively, and no increase in excitability in a performance-matched control experiment in which subjects were required to progressively ramp up motor output, suggesting that excitability changes do not directly relate to changes in performance. In addition, control experiments showed that the increases in excitability could not be attributed to correcting visual errors or changes in kinematics or EMG. Overall, the results are consistent with the idea that changes in corticospinal excitability are the result of learning rather than performance changes or errors.

Many studies have measured MEP changes after various forms of intervention with respect to motor output, including motor learning. The critical question examined here is what changes in excitability signify. Do changes in excitability relate to behavioral changes or learning, or are they merely epiphenomenal? The experimental appeal of MEPs is that they may be measured noninvasively and thus can be used in human studies. The pervasive assumption appears to be that an increase in MEP is behaviorally relevant because it should make it easier to then voluntarily recruit motoneurons for execution. Interestingly, however, this assumption has been surprisingly difficult to prove. In several studies, repetitive TMS (rTMS) has been used to alter cortical excitability with inconsequential effects on motor performance (Muellbacher et al. 2000). For example, in one study subjects made repeated fast index finger abductions after 5-Hz rTMS over contralateral M1. The rTMS did not enhance motor performance on any kinematic variable compared with a sham group despite significant differences in MEPs for the two groups (Agostino et al. 2007). In another study, low-frequency rTMS over M1 reduced MEP amplitude in the FDI muscle but had no effect on maximal finger tapping speed, on performance on a grooved pegboard test, on an object grip and lift task, or on visuomotor tracking (Todd et al. 2009). Another study failed to find a relationship between increments in voluntary muscle contraction and changes in cortical excitability (Gelli et al. 2007). Conversely, however, in a study that modulated excitability with practice and ischemic nerve block, motor output was enhanced (Ziemann et al. 2001). Those few studies that arguably have shown a disruptive effect of rTMS over M1 on motor performance have related to higher-order processes rather than execution itself. For example, rTMS over M1 led to impaired grip-force scaling—subjects appeared to have disruption of their memory of the previously lifted object weight (Nowak et al. 2005). Notably, subjects generated forces larger than was required and the effects were bilateral, which suggests that input onto motoneurons may not have been the relevant factor. M1 excitability was not assessed in this study, and the authors conjectured that

rTMS was disrupting sensory inputs into M1 rather than its output. This grip-force scaling effect is consistent with a more recent study that showed larger MEPs when an object that was lifted had been preceded by a heavy rather than a light object; this difference had no apparent effect on ability to scale grip-force in the subsequent lift (Loh et al. 2010). Thus review of the literature presents conflicting evidence with regard to any causal relationship between changes in corticospinal excitability and changes in motor output or performance.

Studying gain adaptation offered the ideal opportunity to dissociate performance- versus learning-related changes in excitability because low and high gains require opposite changes in motor output. For a given target in extrinsic space, after adaptation to a low gain a larger movement with a higher peak velocity is required compared with baseline, and vice versa for a high gain. If MEP amplitude reflects the magnitude of output from M1 then we should have seen opposite changes in excitability in the relevant agonist muscle at low and high gains. Instead we saw large excitability increases for both low- and high-gain adaptation and no excitability changes in a performance-matched training protocol, a result consistent with the studies cited above that showed no clear relationship between excitability and motor output (Agostino et al. 2007; Gelli et al. 2007; Muellbacher et al. 2000; Todd et al. 2009). We conclude that excitability increases following adaptation reflect something other than altered motor output. To attribute these changes to accumulated learning, it was first necessary to control for the possibility that these changes resulted from observation of large sensory prediction errors. We found that in a pseudorandom gain condition, in which subjects had to make continuous online corrections in the setting of large errors, there was only minimal change in excitability. It therefore appears that changes in corticospinal excitability reflect accumulated learning-based modifications in a controller. Interestingly, our analysis of the pseudorandom control task revealed that the modest increases in MEPs in the low-gain condition were likely attributed to the partial adaptation that was evident in the $n + 1$ trial. Overall, these data are consistent with findings in single-unit recording experiments in primates that have shown that motor cortical map expansion does not occur when movements are just repeated; skill learning is also required (Plautz et al. 2000).

It has been shown that there is trial-to-trial motor adaptation under conditions of random perturbation and that such learning is captured by state-space models just as well as learning of a constant perturbation (Diedrichsen et al. 2005; Donchin et al. 2003). Here we found that a pseudorandom gain did not lead to appreciable changes in corticospinal excitability despite evidence for within-trial updating of motor commands. The lack of an effect of visual-to-motor errors on excitability is perhaps not surprising given the lack of direct visual inputs to M1 (Felleman et al. 1997; Lewis and Van Essen 2000), but this finding is also consistent with a variety of studies in human and model systems that report an absence of learning effects in M1 if they are tested before adaptation reaches a steady state, a point when the learned movement is repeated with low variability. Force-field adaptation was only disrupted by TMS over M1 when adaptation had reached asymptote (Orban de Xivry et al. 2011). Similarly, transient disruption of M1 with single-pulse TMS, time-locked to the perturbation of a graspable object, did not impair the online reach-to-grasp correction

(Tunik et al. 2005). Anodal transcranial stimulation (tDCS) over contralateral M1 had an effect on retention of the asymptotic level reached after adaptation to a visuomotor rotation but not on the rate of acquisition (Galea et al. 2011). In a functional MRI study, a learning effect was not detected in M1 for adaptation to either random rotations or force fields; the authors concluded that changes in M1 may only occur when adaptation is allowed to accumulate (Diedrichsen et al. 2005). Similarly, in a single-unit recording study in monkeys, delay-period activity (Paz and Vaadia 2004) and reduced variability in firing rate (Mandelblat-Cerf et al. 2009) in M1 cells were only seen after adaptation to rotation had reached steady state. We recently proposed that these results can be explained by positing that a second form of repetition-associated reinforcement learning occurs in adaptation paradigms and that it may occur in M1 (Huang et al. 2011). In animal models, multiple plastic changes in M1 have been described for skill learning tasks (Kleim et al. 2004; Li et al. 2001; Molina-Luna et al. 2009).

All these results in human and nonhuman animals can be unified by positing that the late reinforcement process in adaptation paradigms and skill learning are mechanistically similar, namely, that they require synaptic changes (in M1 or elsewhere) and that such changes require short-term and long-term potentiation (LTP)-like processes apparent as increases in cortical excitability (Castro-Alamancos and Connors 1997; Ziemann et al. 2004). Thus the increases in corticospinal excitability that we found here for accumulated gain adaptation are consistent with the idea that the changes in motor output required to maintain stable performance may be associated with plastic changes in the motor neuraxis, regardless of the sign of the gain change. Because excitability was assayed through changes in MEPs, it is possible that the effects observed in the present experiments represent changes at the level of M1 cell body synapses, along the length of upper motoneuron (UMN) axons, or at the level of the UMN- α -motoneuron (α MN) synapse in the spinal cord. Indeed, there is persistent debate with regard to which level of the neuraxis is the locus for such learning-dependent changes. It is known from recent magnetic resonance spectroscopy work that focal reductions in GABA inhibition occur in sensorimotor cortex during motor learning (Floyer-Lea et al. 2006), and stimulation studies have shown that the degree of learning in M1 is correlated with the ability to modulate GABA inhibition (Stagg et al. 2011), which may be artificially inhibited with stimulation techniques such as anodal tDCS (Stagg et al. 2009). Likewise, some have shown that learning has little effect on corticofugal axonal excitability (Classen et al. 1998) or spinal excitability (Kleim et al. 2002; Remple et al. 2001). Learning-related changes have been detected, however, at spinal levels, too, characterized by modulated changes in the H reflex (Meunier et al. 2007; Winkler et al. 2012; Wolpaw 2010). So far, the specific involvement of cortical versus spinal levels in motor learning remains unknown. The evidence clearly supports the notion that spinal-level reflex circuitry can be conditioned in relatively simple tasks (Thompson et al. 2009) or even by stimulation of the motor cortex (Wang et al. 2012). Empirical data suggest that voluntary acquisition of complex visuomotor skills relies on the direct involvement of motor cortex (Pruszynski et al. 2011; Pruszynski and Scott 2012). Our study was limited by the absence of spinal-level excitability measurements, limiting

our ability to isolate the precise location in the neuraxis at which our corticospinal excitability changes occurred. Regardless of the location of excitability change (M1 vs. UMN axon vs. UMN- α MN synapse) or the underlying neuronal mechanism (increased excitation vs. decreased inhibition), the present study demonstrates that visuomotor adaptation induces short-term, sign-independent facilitation of the corticospinal system. An interesting follow-up study would be to use the same gain adaptation paradigm (along with spinal-level assays of excitability) to test for longer-lasting effects across separate days, at varying stimulation intensities (i.e., 115% vs. 120% resting motor threshold) and background EMG levels [i.e., force output at 0 N (rest), 1 N, 3 N, etc.].

Our finding of increases in corticospinal excitability for both increases and decreases in gain is consistent with those previous studies that have shown no behavioral consequence of changes in MEP magnitude (Agostino et al. 2007; Gelli et al. 2007; Todd et al. 2009). We conclude that caution is required when reporting changes in MEP magnitude as having behavioral significance, especially in the context of neurorehabilitation. Had adaptation to the two oppositely signed gains shown a differential effect on excitability, then perhaps more of a case could have been made for using manipulations of visual feedback to enhance cortical excitability and perhaps aid voluntary recruitment. Given our results, however, we conclude that changes in corticospinal excitability are a marker for learning-related processes and should not in and of themselves be considered relevant to motor performance. That said, it is possible that if excitability is abnormally depressed, like after stroke, then methods to enhance excitability might improve performance (Hummel et al. 2005; Hummel and Cohen 2006; Khedr et al. 2005; Tanaka et al. 2009). This consideration leads to the interesting possibility that VR adaptation paradigms might indirectly benefit patients after stroke by increasing excitability, which may then enhance performance in unrelated motor tasks.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: H.F.B., S.S., S.V.A., J.W.K., and E.T. conception and design of research; H.F.B., S.S., and E.T. performed experiments; H.F.B., S.V.A., and E.T. analyzed data; H.F.B., S.V.A., J.W.K., and E.T. interpreted results of experiments; H.F.B. prepared figures; H.F.B., J.W.K., and E.T. drafted manuscript; H.F.B., S.V.A., J.W.K., and E.T. edited and revised manuscript; H.F.B., S.S., S.V.A., J.W.K., and E.T. approved final version of manuscript.

REFERENCES

Adkins DL, Boychuk J, Remple MS, Kleim JA. Motor training induces experience-specific patterns of plasticity across motor cortex and spinal cord. *J Appl Physiol* 101: 1776–1782, 2006.

- Agostino R, Iezzi E, Dinapoli L, Gilio F, Conte A, Mari F, Berardelli A. Effects of 5 Hz subthreshold magnetic stimulation of primary motor cortex on fast finger movements in normal subjects. *Exp Brain Res* 180: 105–111, 2007.
- Aranyi Z, Mathis J, Hess CW, Rosler KM. Task-dependent facilitation of motor evoked potentials during dynamic and steady muscle contractions. *Muscle Nerve* 21: 1309–1316, 1998.
- Bindman LJ, Lippold OC, Redfearn JW. The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects. *J Physiol* 172: 369–382, 1964.
- Castro-Alamancos MA, Connors BW. Distinct forms of short-term plasticity at excitatory synapses of hippocampus and neocortex. *Proc Natl Acad Sci USA* 94: 4161–4166, 1997.
- Cirillo J, Todd G, Semmler JG. Corticomotor excitability and plasticity following complex visuomotor training in young and old adults. *Eur J Neurosci* 34: 1847–1856, 2011.
- Classen J, Liepert J, Wise SP, Hallett M, Cohen LG. Rapid plasticity of human cortical movement representation induced by practice. *J Neurophysiol* 79: 1117–1123, 1998.
- Creutzfeldt OD, Fromm GH, Kapp H. Influence of transcortical d-c currents on cortical neuronal activity. *Exp Neurol* 5: 436–452, 1962.
- Datta AK, Harrison LM, Stephens JA. Task-dependent changes in the size of response to magnetic brain stimulation in human first dorsal interosseous muscle. *J Physiol* 418: 13–23, 1989.
- Diedrichsen J, Hashambhoy Y, Rane T, Shadmehr R. Neural correlates of reach errors. *J Neurosci* 25: 9919–9931, 2005.
- Donchin O, Francis JT, Shadmehr R. Quantifying generalization from trial-by-trial behavior of adaptive systems that learn with basis functions: theory and experiments in human motor control. *J Neurosci* 23: 9032–9045, 2003.
- Felleman DJ, Burkhalter A, Van Essen DC. Cortical connections of areas V3 and VP of macaque monkey extrastriate visual cortex. *J Comp Neurol* 379: 21–47, 1997.
- Flament D, Goldsmith P, Buckley CJ, Lemon RN. Task dependence of responses in first dorsal interosseous muscle to magnetic brain stimulation in man. *J Physiol* 464: 361–378, 1993.
- Floyer-Lea A, Wylezinska M, Kincses T, Matthews PM. Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *J Neurophysiol* 95: 1639–1644, 2006.
- Galea JM, Vazquez A, Pasricha N, de Xivry JJ, Celnik P. Dissociating the roles of the cerebellum and motor cortex during adaptive learning: the motor cortex retains what the cerebellum learns. *Cereb Cortex* 21: 1761–1770, 2011.
- Gallasch E, Christova M, Krenn M, Kossev A, Rafolt D. Changes in motor cortex excitability following training of a novel goal-directed motor task. *Eur J Appl Physiol* 105: 47–54, 2009.
- Gelli F, Del Santo F, Popa T, Mazzocchio R, Rossi A. Factors influencing the relation between corticospinal output and muscle force during voluntary contractions. *Eur J Neurosci* 25: 3469–3475, 2007.
- Huang VS, Haith A, Mazzoni P, Krakauer JW. Rethinking motor learning and savings in adaptation paradigms: model-free memory for successful actions combines with internal models. *Neuron* 70: 787–801, 2011.
- Hummel F, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain* 128: 490–499, 2005.
- Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol* 5: 708–712, 2006.
- Jensen JL, Marstrand PC, Nielsen JB. Motor skill training and strength training are associated with different plastic changes in the central nervous system. *J Appl Physiol* 99: 1558–1568, 2005.
- Kasai T, Yahagi S. Motor evoked potentials of the first dorsal interosseous muscle in step and ramp index finger abduction. *Muscle Nerve* 22: 1419–1425, 1999.
- Keel JC, Smith MJ, Wasserman EM. A safety screening questionnaire for transcranial magnetic stimulation. *Clin Neurophysiol* 112: 720, 2000.
- Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology* 65: 466–468, 2005.
- Kleim JA, Barbay S, Cooper NR, Hogg TM, Reidel CN, Remple MS, Nudo RJ. Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiol Learn Mem* 77: 63–77, 2002.
- Kleim JA, Hogg TM, VandenBerg PM, Cooper NR, Bruneau R, Remple M. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. *J Neurosci* 24: 628–633, 2004.

- Koenke S, Lutz K, Herwig U, Ziemann U, Jancke L.** Extensive training of elementary finger tapping movements changes the pattern of motor cortex excitability. *Exp Brain Res* 174: 199–209, 2006.
- Koski L, Mernar TJ, Dobkin BH.** Immediate and long-term changes in corticomotor output in response to rehabilitation: correlation with functional improvements in chronic stroke. *Neurorehabil Neural Repair* 18: 230–249, 2004.
- Krakauer JW.** Avoiding performance and task confounds: multimodal investigation of brain reorganization after stroke rehabilitation. *Exp Neurol* 204: 491–495, 2007.
- Lewis JW, Van Essen DC.** Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J Comp Neurol* 428: 112–137, 2000.
- Li CS, Padoa-Schioppa C, Bizzi E.** Neuronal correlates of motor performance and motor learning in the primary motor cortex of monkeys adapting to an external force field. *Neuron* 30: 593–607, 2001.
- Loh MN, Kirsch L, Rothwell JC, Lemon RN, Davare M.** Information about the weight of grasped objects from vision and internal models interacts within the primary motor cortex. *J Neurosci* 30: 6984–6990, 2010.
- Mandelblat-Cerf Y, Paz R, Vaadia E.** Trial-to-trial variability of single cells in motor cortices is dynamically modified during visuomotor adaptation. *J Neurosci* 29: 15053–15062, 2009.
- Meunier S, Kwon J, Russmann H, Ravindran S, Mazzocchio R, Cohen L.** Spinal use-dependent plasticity of synaptic transmission in humans after a single cycling session. *J Physiol* 579: 375–388, 2007.
- Molina-Luna K, Pekanovic A, Rohrich S, Hertler B, Schubring-Giese M, Rioult-Pedotti MS, Luft AR.** Dopamine in motor cortex is necessary for skill learning and synaptic plasticity. *PLoS One* 4: e7082, 2009.
- Muellbacher W, Ziemann U, Borojerdi B, Cohen L, Hallett M.** Role of the human motor cortex in rapid motor learning. *Exp Brain Res* 136: 431–438, 2001.
- Muellbacher W, Ziemann U, Borojerdi B, Hallett M.** Effects of low-frequency transcranial magnetic stimulation on motor excitability and basic motor behavior. *Clin Neurophysiol* 111: 1002–1007, 2000.
- Ni Z, Takahashi M, Yamashita T, Liang N, Tanaka Y, Tsuji T, Yahagi S, Kasai T.** Functional demanded excitability changes of human hand motor area. *Exp Brain Res* 170: 141–148, 2006.
- Nowak DA, Voss M, Huang YZ, Wolpert DM, Rothwell JC.** High-frequency repetitive transcranial magnetic stimulation over the hand area of the primary motor cortex disturbs predictive grip force scaling. *Eur J Neurosci* 22: 2392–2396, 2005.
- Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9: 97–113, 1971.
- Orban de Xivry JJ, Criscimagna-Hemminger SE, Shadmehr R.** Contributions of the motor cortex to adaptive control of reaching depend on the perturbation schedule. *Cereb Cortex* 21: 1475–1484, 2011.
- Paninski L, Fellows MR, Hatsopoulos NG, Donoghue JP.** Spatiotemporal tuning of motor cortical neurons for hand position and velocity. *J Neurophysiol* 91: 515–532, 2004.
- Pascual-Leone A, Grafman J, Hallett M.** Modulation of cortical motor output maps during development of implicit and explicit knowledge. *Science* 263: 1287–1289, 1994.
- Pascual-Leone A, Nguyet D, Cohen LG, Brasil-Neto JP, Cammarota A, Hallett M.** Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J Neurophysiol* 74: 1037–1045, 1995.
- Paz R, Vaadia E.** Learning-induced improvement in encoding and decoding of specific movement directions by neurons in the primary motor cortex. *PLoS Biol* 2: E45, 2004.
- Plautz EJ, Milliken GW, Nudo RJ.** Effects of repetitive motor training on movement representations in adult squirrel monkeys: role of use versus learning. *Neurobiol Learn Mem* 74: 27–55, 2000.
- Pruszynski JA, Kurtzer I, Nashed JY, Omrani M, Brouwer B, Scott SH.** Primary motor cortex underlies multi-joint integration for fast feedback control. *Nature* 478: 387–390, 2011.
- Pruszynski JA, Scott SH.** Optimal feedback control and the long-latency stretch response. *Exp Brain Res* 218: 341–359, 2012.
- Purpura DP, McMurtry JG.** Intracellular activities and evoked potential changes during polarization of motor cortex. *J Neurophysiol* 28: 166–185, 1965.
- Rapisarda G, Bastings E, de Noordhout AM, Pennisi G, Delwaide PJ.** Can motor recovery in stroke patients be predicted by early transcranial magnetic stimulation? *Stroke* 27: 2191–2196, 1996.
- Raptis H, Burtet L, Forget R, Feldman AG.** Control of wrist position and muscle relaxation by shifting spatial frames of reference for motoneuronal recruitment: possible involvement of corticospinal pathways. *J Physiol* 588: 1551–1570, 2010.
- Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA.** Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behav Brain Res* 123: 133–141, 2001.
- Stagg CJ, Bachtier V, Johansen-Berg H.** The role of GABA in human motor learning. *Curr Biol* 21: 480–484, 2011.
- Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, Morris PG, Matthews PM, Johansen-Berg H.** Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J Neurosci* 29: 5202–5206, 2009.
- Swayne OB, Rothwell JC, Ward NS, Greenwood RJ.** Stages of motor output reorganization after hemispheric stroke suggested by longitudinal studies of cortical physiology. *Cereb Cortex* 18: 1909–1922, 2008.
- Tanaka S, Hanakawa T, Honda M, Watanabe K.** Enhancement of pinch force in the lower leg by anodal transcranial direct current stimulation. *Exp Brain Res* 196: 459–465, 2009.
- Thompson AK, Chen XY, Wolpaw JR.** Acquisition of a simple motor skill: task-dependent adaptation plus long-term change in the human soleus H-reflex. *J Neurosci* 29: 5784–5792, 2009.
- Todd G, Rogasch NC, Flavel SC, Ridding MC.** Voluntary movement and repetitive transcranial magnetic stimulation over human motor cortex. *J Appl Physiol* 106: 1593–1603, 2009.
- Tunik E, Frey SH, Grafton ST.** Virtual lesions of the anterior intraparietal area disrupt goal-dependent on-line adjustments of grasp. *Nat Neurosci* 8: 505–511, 2005.
- Vang C, Dunabin D, Kilpatrick D.** Correlation between functional and electrophysiological recovery in acute ischemic stroke. *Stroke* 30: 2126–2130, 1999.
- Wang Y, Chen Y, Chen L, Wolpaw JR, Chen XY.** Cortical stimulation causes long-term changes in H-reflexes and spinal motoneuron GABA receptors. *J Neurophysiol* 108: 2668–2678, 2012.
- Winkler T, Mergner B, Szecsi J, Bender A, Straube A.** Spinal and cortical activity-dependent plasticity following learning of complex arm movements in humans. *Exp Brain Res* 219: 267–274, 2012.
- Wolpaw JR.** What can the spinal cord teach us about learning and memory? *Neuroscientist* 16: 532–549, 2010.
- Ziemann U, Illic TV, Pauli C, Meintzschel F, Ruge D.** Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci* 24: 1666–1672, 2004.
- Ziemann U, Muellbacher W, Hallett M, Cohen LG.** Modulation of practice-dependent plasticity in human motor cortex. *Brain* 24: 1171–1181, 2001.